DYSAUTONOMIA INTERNATIONAL

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1601
Rockville, MD 20852

**RE: Docket ID: FDA-2012-N-0967-0595**

To Whom It May Concern:

On behalf of the Board of Directors of Dysautonomia International, I am writing in regard to the PDUFA V patient-focused drug development public meetings that are planned for FY 2013-2017, to request that "autonomic nervous system disorders" be prioritized as a meeting focus area.

Dysautonomia International is the leading non-profit organization dedicated to improving the lives of individuals living with autonomic nervous system disorders, collectively known as "dysautonomia." This is accomplished by supporting research, physician education, patient empowerment and public awareness programs.

As explained below, autonomic nervous system disorders fit well within the criteria identified in FDA's October 8, 2014 notice. Inclusion of this topic is important, as autonomic nervous system disorder are largely misunderstood and under-recognized by the medical and research community. Based on current research trends, the FDA is likely to see applications for drug and device approvals related to disorders of the autonomic nervous system in the next few years.

## I. Disease areas that are chronic, symptomatic, or affect functioning and activities of daily living.

Most autonomic nervous system disorders are chronic, very symptomatic, and significantly affect functioning and activities of daily living. Such disorders include postural orthostatic tachycardia syndrome (POTS), pure autonomic failure (PAF), multiple system atrophy (MSA), familial dysautonomia (FD) and autonomic neuropathies secondary to diabetes, Sjogren's syndrome, Celiac

disease, paraneoplastic syndrome, and many other underlying pathologies. Autonomic nervous system dysfunction also occurs secondary to Parkinson's, multiple sclerosis, spinal cord injury, and other CNS diseases. While the underlying pathologies of these diseases differ, the symptoms and impact on a patient's ability to function are very similar.

The autonomic nervous system is involved in regulating multiple bodily systems. Impairments to the autonomic nervous system can cause a wide range of symptoms including, tachycardia, bradycardia, very low or high blood pressure, dizziness, orthostatic intolerance, syncope and injuries as a consequence of syncope, cognitive impairment, extreme fatigue, weakness, insomnia, unrefreshing sleep, nausea, vomiting, reflux, gastroparesis, diarrhea, chest pain, shortness of breath, temperature dysregulation, diminished or excessive sweating, dry eyes, dry mouth, difficulty swallowing, blood pooling in extremities, headaches, tremulousness, loss of bladder control, loss of sexual functioning and more.

The wide variety of symptoms that occur when the autonomic nervous system is impaired greatly interfere with patients' functioning and quality-of-life. Difficulty with standing, sitting, walking, driving and any upright activity is common. Falls caused by syncopal episodes can cause serious injury and in some cases death. Researchers compare the quality-of-life in POTS to what is seen in congestive heart failure, COPD, and kidney failure patients on dialysis. A study on the quality-of-life in patients with spinal cord paralysis found that these patients ranked regaining their autonomic nervous system function as more important than regaining their ability to walk.

## II. Disease areas that have a severe impact on identifiable subpopulations.

Different disorders of the autonomic nervous system impact different subpopulations, but all have a severe impact on the patients suffering from these conditions.

POTS affects an estimated 500,000 – 1,000,000 Americans. 85% of patients are female and most are between the ages of 12 and 40. Onset in adolescence is common. Mayo Clinic's Chief of Pediatric & Adolescent Medicine, Dr. Philip Fischer, estimates that 1 in 100 teens develops POTS before adulthood. 25% of POTS patients are so disabled they cannot attend school or work. The most severely disabled POTS patients can become bedridden, require nutrition through nasogastric or jejunal tubes, use of a reclining wheelchair, and/or chest ports to administer regular intravenous saline.

Pure autonomic failure (PAF), multiple system atrophy (MSA) and autonomic dysfunction secondary to Parkinson's primarily impacts older adults. PAF patients have a slowly progressive disease, Parkinson's a moderately progressive disease and MSA is a rapidly progressive disease. The progressive autonomic dysfunction seen in these patients is a major source of disability and eventual mortality.

About 25% of all diabetics develop autonomic neuropathy. Patients with diabetic autonomic neuropathy tend to be those who have had poorly controlled diabetes for many years. Once diabetic cardiac autonomic neuropathy occurs, patients have a 50% risk of dying within five years.

Autonomic neuropathy impacts an identifiable subset of patients living with Sjogren's, Celiac disease and multiple sclerosis. In these patients, the disability cause by the autonomic neuropathy is typically more disabling than the other symptoms of their disease.

**III. Disease areas for which there are currently no therapies or very few therapies; or the available therapies do not directly affect how a patient feels, functions or survives:**

Midodrine and the recently approved droxidopa (Northera) are the only two drugs specifically approved to treat an autonomic nervous system disorder – orthostatic hypotension.

Other drugs are used off label in an attempt to manage the many symptoms that occur in patients with disorders of the autonomic nervous system. Since these drugs were not developed for specific disorders of the autonomic nervous system, they often don't work well or they cause intolerable side effects. Examples include beta-blockers, flourinef, desmopressin and phenylephrine.

There are no FDA approved drugs to treat postural orthostatic tachycardia syndrome (POTS), which impacts 500,000 - 1,000,000 Americans. Recent research indicates that a large subset of the POTS population appears to have an autoimmune etiology. FDA may be asked to review new drug applications or label change applications for immune modulating therapies to treat POTS in the next few years. It is important for the FDA to understand POTS and autonomic dysfunction as a whole before considering these applications.

**IV. Disease areas for which aspects of the disease are not formally captured in clinical trials:**

The impact of autonomic dysfunction on quality-of-life is rarely, if ever, accurately captured in clinical trials. The very few clinical trials that have occurred on drugs meant to treat autonomic dysfunction tend to focus on blood pressure, heart rate and other easy to measure endpoints. These endpoints do not necessarily correlate with the functional disability seen in our patient population. A dysautonomia patient with perfect 120/80 upright blood pressure may have more functional disability than someone with a lower 90/60 blood pressure.

What matters to a dysautonomia patient is whether they can stand up long enough to put their laundry away, if their coat-hanger pain has improved enough so that they can walk the dog, if they can eat a normal meal without choking, vomitting, nausea, and bloating, or if they can sleep through the night without being awakened by tachycardia, chest pain and sheet drenching night sweats.

Given the wide range of disability seen in each autonomic disorder, we believe that the stage of the disease and baseline disability need to be more accurately characterized in clinical trials related to autonomic disorders. A drug that may provide a significant benefit to a patient who has early, mild disability, may not provide any benefit to a patient who has advanced illness.

Midodrine is at risk of being removed from US shelves by the FDA, in part, because the endpoints used in prior midodrine studies do not reflect the actual benefit orthostatic hypotension patients receive from using midodrine. FDA is currently reviewing the NDA for midodrine, one of the most important drugs for our patient community. It is used successfully by physicians to treat a wide variety of autonomic disorders. Midodrine is the perfect example of a drug that has very practical and substantial quality-of-life benefits for our patient population, which are not being identified and measured in the clinical trial data submitted to the FDA. One could not think of a better example of why PDUFA V's mandate is so important to patients.

## V. Conclusion

In conclusion, the dysautonomia patient population would greatly benefit from the opportunity to have public meetings with the FDA to discuss symptoms, how daily lives are impacted by these conditions, response to currently available treatments and a focus on what interventions are still needed. We ask that you please consider "autonomic nervous system disorders" as a potential candidate for inclusion on the list of disease areas.

Thank you for the opportunity to submit this comment regarding FDA's patient-focused drug development initiative.

Sincerely,

Lauren E. Stiles, Esq.
President, Dysautonomia International